

Serial No: 09/512,363

Ref No. PF396P1

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(SEQ ID NO:7)). On October 7, 1997, deposits of plasmid DNAs encoding TR11, TR11SV1, and TR11SV2 were made at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession numbers 209341, 209342, and 209343, respectively. The nucleotide sequences shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5, respectively) were obtained by sequencing cDNA clones (Clone ID HT1EAC71, HT5EA78 and HCFAZ22, respectively) containing the same amino acid coding sequences as the clones in ATCC Accession Nos. 209341, 209342, and 209343, respectively. The deposited clone encoding TR11 is contained in the pCMVSPORT3.0 plasmid (Life Technologies, Rockville, MD). The deposited clone encoding TR11SV1 is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The deposited clone encoding TR11SV2 is contained in the pSport1 plasmid (Life Technologies, Rockville, MD).

Please replace the paragraph starting on line 33 of Page 11 and ending on page 12, line 5, with the following amended paragraph.

B²

The determined nucleotide sequence of the TR11 cDNA of Figures 1A and 1B (SEQ ID NO:1) contains an open reading frame encoding a protein of about 234 amino acid residues, with a single potential predicted leader sequence of about 25 amino acid residues, and a deduced molecular weight of about 25,113 Da. The amino acid sequence of the potential predicted mature TR11 receptor is shown in Figures 1A and 1B, from amino acid residue about 26 to residue about 234 (amino acid residues 1 to 209 in SEQ ID NO:2). The TR11 protein shown in Figures 1A and 1B (SEQ ID NO:2) is about 58.6% identical and about 74.1% similar to the murine mGIR receptor protein shown in SEQ ID NO:7 (see Figures 1A and 1B) using the computer program "Bestfit".

Please replace the paragraph spanning lines 1-36 of page 40 with the following amended paragraph.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example,

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homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the TR11, TR11SV1 and/or TR11SV2 polypeptide sequences (e.g., those recited in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, or contained in the respective TR11, TR11SV1 and TR11SV2 polypeptides encoded by the respective clones HHEAC71, HT5EA78 and HCFAZ22). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a TR11, TR11SV1 or TR11SV2 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a TR11-Fc, TR11SV1-Fc or TR11SV2 Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more TR11, TR11SV1, TR11SV2 polypeptides of the invention are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include, but are not limited to, those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple TR11, TR11SV1, TR11SV2 polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

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Please replace the paragraph beginning on line 33 of page 78 and ending on page 79, line 9 with the following amended paragraph.

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As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 1A and 1B (SEQ ID NO:2), Figures 2A and 2B (SEQ ID NO:4), and/or Figures 3A and 3B (SEQ ID NO:6), the amino acid sequence encoded by deposited cDNA clones HHEAC71, HT5EA78 and HCFAZ22, respectively, or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

Please replace the paragraph spanning lines 17-32 of page 136 with the following amended paragraph

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In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in TR11, TR11SV1 and/or TR11SV2, or the complementary strand thereof, and/or to nucleotide sequences contained in the deposited clones HHEAC71, HT5EA78 and HCFAZ22, respectively. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456

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